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19MAR E43395-1 D02944
P01/77 0.00- 9906328.1

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The Patent Office

Cardiff Road
Newport
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1. Your reference

SMC 60344/GB/P

2. Patent application number

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9906328.1

19 MAR 1999

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Zeneca Limited
15 Stanhope Gate
London
W1Y 6LN

Patents ADP number (if you know it)

6254007002

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom ✓

4. Title of the invention

2'-Substituted RNA Preparation

5. Name of your agent (if you have one)

REVELL, Christopher

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

Zeneca Specialties
PO Box 42, Hexagon House
Blackley, Manchester M9 8ZS
United Kingdom

Patents ADP number (if you know it)

6969885001 15081003

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Country

Priority application number
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Date of filing
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Number of earlier application

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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

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8

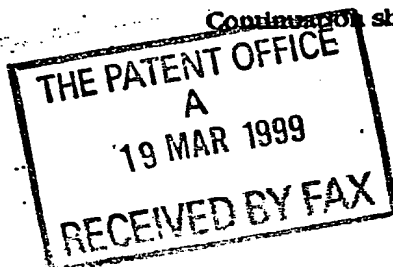
Claim(s)

2/ 81

Abstract

1/

Drawing(s)



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Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

11.

I/We request the grant of a patent on the basis of this application.

Signature

Kirsty Pinder

Date 19/3/99

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12. Name and daytime telephone number of person to contact in the United Kingdom

KIRSTY PINDER 0161 721 1361

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DUPLICATE

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2'-SUBSTITUTED RNA PREPARATION

The present invention relates to a process for preparing 2'-O-substituted nucleosides, and more particularly to a process for the preparation of 2'-O-substituted uridine and cytidine.

The possibility that synthetic oligonucleotides might be effective inhibitors of gene expression and be used as chemotherapeutic agents has stimulated much research work in recent years. In order to avoid their degradation by cellular nucleases, it is essential that such oligonucleotides should be modified. Modifications can be made to the internucleotide linkages, the base residues and the sugar residues. A large number of oligonucleotide analogues in which the internucleotide linkages have been modified, especially as phosphorothioates with non-bridging sulphur atoms, have been described. Several of these phosphorothioate analogues are promising drug candidates that are now undergoing clinical trials. However, phosphorothioates do have some disadvantages. Thus, they do not display optimal RNA-binding properties and they also have a tendency to bind to proteins in a non-specific manner. Possible base modifications are clearly limited as they must not lead to a significant decrease in hybridisation properties. Recently, considerable interest has been directed towards the modification of the sugar residues. One particular type of modification involves the introduction of 2'- α -alkoxy groups (as in 2'-O-alkyl-oligoribonucleotides). While, in general, small alkoxy groups (such as methoxy) promote better hybridisation properties with complementary ribonucleic acids (RNA), nuclease resistance tends to increase with an increase in the size of the alkoxy group. 2-Methoxyethoxy has emerged as an alkoxy group that confers both good hybridisation properties and high nuclease resistance. It therefore seems likely that 2'-O-(2-methoxyethyl)-ribonucleosides will be incorporated into a second generation of potential oligonucleotide chemotherapeutic agents. For this reason, the development of convenient methods for the preparation of 2'-O-(2-methoxyethyl)-ribonucleosides has become a matter of much importance.

The preparation of 2'-O-(2-methoxyethyl)-ribonucleosides, starting from D-ribose, has previously been described. These preparations involved the use of protecting groups and required a relatively large number of steps. For example, 2'-O-(2-methoxyethyl)-5-methyluridine was prepared by Martin, P. *Helv. Chim. Acta* 1995, 78, 486-504 from D-ribose in 10 steps and in 33% overall yield. A later report by McGee and Zhai in *Abstracts of American Chemical Society National Meeting, Division of Organic Chemistry, March 1996* paper 253 revealed a much more convenient procedure for the preparation of 2'-O-alkyl derivatives of the main pyrimidine ribonucleosides. Thus, when 5'-O-(4,4'-dimethoxytrityl)-2,2'-anhydro-1- β -D-arabinofuranosyluracil was heated with magnesium methoxide in N,N-dimethylformamide (DMF) at 100°C, 5'-O-(4,4'-dimethoxytrityl)-2'-O-methyluridine was obtained in 94% yield. Somewhat lower yields of the corresponding 5'-

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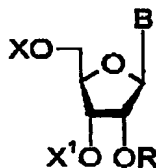
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O-ethyl-, 5'-O-(n-propyl)- and 5'-O-allyl-uridine derivatives were obtained in the reactions between the same substrate and the appropriate magnesium alkoxides. It was also reported that magnesium alkoxides could be replaced by calcium alkoxides.

Ross et al reported in Nucleosides and Nucleotides, 1997, 16, 1641-3 that when unprotected 2,2'-anhydro-1- β -D-arabinofuranosyluracil was heated with a twofold excess of trimethyl borate and a stoichiometric quantity of trimethyl orthoformate in methanol at 150°C, under pressure, for 42 h, 2'-O-methyluridine was obtained in 86% isolated yield. 2'-O-Methyl-5-methyluridine was similarly prepared from 2,2'-anhydro-5-methyl-(1- β -D-arabinofuranosyluracil) by the borate ester procedure and, although no experimental details were provided, the preparation of 2'-O-methylcytidine was also reported. The yield of 2'-O-alkyl-uridine was stated to decrease with increasing alcohol size.

It remains desirable to identify additional or alternative routes for the preparation of 2'-O-substituted nucleosides.

According to the present invention, there is provided a process for the preparation of a compound of formula (1):



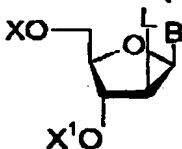
wherein:

X, and X' are each independently H or a protecting group;

B is a base; and

R is an alkyl, alkoxyalkyl, alkenyl, or alkynyl group, each of which may be optionally substituted;

which comprises reacting a compound of formula (2):



wherein

L is a leaving group; and

B, X and X' are as defined above

with a compound of formula $Al(OR)_3$ wherein R is as defined above, under substantially anhydrous conditions.

When R is alkenyl, the alkenyl group is often a C_{1-4} alkenyl group, especially an allyl or crotyl group. When R represents alkyl, the alkyl group is preferably a C_{1-4} alkyl, and most preferably a methyl or ethyl group. When R represents alkoxyalkyl, the alkoxyalkyl group is often a C_{1-4} alkoxy C_{1-4} alkyl group, and preferably a methoxyethyl group. When R is alkynyl, the alkynyl group is often a C_{1-4} alkynyl group, especially a

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propargyl group. The alkyl, alkenyl, alkynyl and alkoxyalkyl groups may themselves be substituted by one or more substituents, particularly halogen, especially F, Cl or Br, and amino substituents.

5 Examples of protecting groups which can be represented by X and X' include acid labile protecting groups, particularly trityl and substituted trityl groups such as dimethoxytrityl and 9-phenylxanthen-9-yl groups; acid-labile acetal protecting groups, particularly 1-(2-fluorophenyl)-4-methoxypiperidine-4-yl (Fmp); and base labile-protecting groups such as acyl groups, commonly comprising up to 16 carbon atoms, such as ethanoyl groups or fatty alkanoyl groups, including particularly linear or branched C₆₋₁₆ alkanoyl groups, such as lauroyl groups; benzoyl and substituted benzoyl groups, such as alkyl, commonly C₁₋₄ alkyl-, and halo, commonly chloro or fluoro, substituted benzoyl groups.

10 Other suitable protecting groups include those derived from gamma keto acids, such as levulinoyl groups and substituted levulinoyl groups. Substituted levulinoyl groups include 5-halo-levulinoyl, such as 5,5,5-trifluorolevulinoyl and benzoylpropionyl groups; and silyl and siloxane ethers, such as alkyl, commonly C₁₋₄ alkyl, and aryl, commonly phenyl, silyl ethers, particularly trialkylsilyl groups, often tri(C₁₋₄-alkyl)silyl groups, such as tertiary butyl dimethyl silyl and tertiary butyl diphenyl silyl groups.

15 Bases which can be represented by B include purines, especially adenine (A) and guanine (G), and pyrimidines, especially thymine (T), cytosine (C), and uracil (U), and substituted derivatives thereof. Examples of substituents which may substitute the bases, in addition to protecting groups, include alkyl, especially C₁₋₄-alkyl, particularly methyl; halogen, particularly Cl or Br; amino; alkenyl, especially C₁₋₄-alkenyl and particularly allyl; alkoxyalkyl, especially C₁₋₄alkoxyC₁₋₄alkyl, particularly methoxyalkyl; and alkynyl, particularly propargyl, substituents. The alkyl, alkenyl, alkynyl and alkoxyalkyl groups may themselves be substituted by one or more substituents, particularly halogen, especially F, Cl or Br, and amino substituents.

20 In addition to the presence of protecting groups X and X', bases employed in present invention may also be protected where necessary by suitable protecting groups. Protecting groups employed are those known in the art for protecting such bases. For example, A and/or C can be protected by benzoyl, including substituted benzoyl, for example alkyl- or alkoxy-, often C₁₋₄ alkyl- or C₁₋₄alkoxy-, benzoyl; pivaloyl; and amidine, particularly dialkylaminomethylene, preferably di(C₁₋₄-alkyl) aminomethylene such as dimethyl or dibutyl aminomethylene. G may be protected by a phenyl group, including substituted phenyl, for example 2,5-dichlorophenyl and also by an isobutyryl group. T and U generally are not protected, but in certain embodiments they may advantageously be protected, for example at O4 by a phenyl group, including substituted phenyl, for example 2,4-dimethylphenyl or at N3 by a pivaloyloxymethyl, benzoyl, alkyl or alkoxy substituted benzoyl, such as C₁₋₄ alkyl- or C₁₋₄ alkoxybenzoyl.

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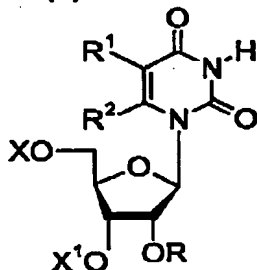
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In certain embodiments, X and X' comprise a single protecting group which protects both the 3' and 5' positions. Examples of such groups include disiloxanes, especially tetraalkyldisiloxanes, such as tetraisopropylidisiloxane.

Leaving groups which can be represented by L include those leaving groups which can be displaced by a nucleophile of formula RO^- . Examples of preferred leaving groups include groups of formula $-OSO_2CH_3$, $-OSO_2CF_3$, Cl, Br, I, O-Mesyl, O-Brosyl and O-Tosyl groups.

In certain preferred embodiments, the leaving group comprises the base, B, chemically bonded to the 2'-position, commonly via an oxygen or sulphur atom or a group of formula $-NR^x-$, wherein R^x is H or a C_{1-8} alkyl or aryl, such as a phenyl, group. Most preferably, the base is uracil bonded to the 2'-position via an oxygen atom.

Accordingly, a second aspect of the present invention provides a process for the preparation of a compound of formula (3):



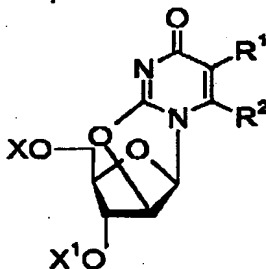
wherein:

X and X' are as defined above;

R^1 and R^2 are each independently H, alkyl, alkenyl, alkynyl, or halogen; and

R is an alkyl, alkoxyalkyl, alkenyl, or alkynyl group, each of which may be optionally substituted;

which comprises the reaction of a compound of formula (4)



wherein

X, X', R^1 and R^2 are as defined above;

with a compound of formula $Al(OR)_3$ wherein R is as defined above, under substantially anhydrous conditions.

When either of R^1 and R^2 is alkenyl, the alkenyl group is often a C_{1-4} alkenyl group, especially an allyl or crotyl group. When either of R^1 and R^2 represents alkyl, the alkyl

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group is preferably a C₁₋₄ alkyl, and most preferably a methyl or ethyl group. When either of R¹ and R² represents alkoxyalkyl, the alkoxyalkyl group is often a C₁₋₄ alkoxyC₁₋₄ alkyl group, and preferably a methoxyethyl group. When either of R¹ and R² is alkynyl, the alkynyl group is often a C₁₋₄ alkynyl group, especially a propargyl group. The alkyl, alkenyl and alkynyl groups represented by R¹ or R² may be substituted by one or more substituents, particularly halogen, especially F, Cl or Br, and amino substituents. When either of R¹ and R² is halogen the halogen is preferably Cl, Br or I. Most preferably, both of R¹ and R² represent H, or R¹ represents C₁₋₄ alkyl and R² represents H.

The process according to the present invention takes place in the presence of a suitable substantially anhydrous solvent. Examples of suitable solvents include halocarbons such as chloroform, 1,2-dichloroethane and chlorobenzene; esters, particularly alkyl esters such as ethyl acetate, and methyl or ethyl propionate; amides such as N-methylpyrrolidinone, dimethylformamide and particularly dimethylacetamide; lower alkyl, for example C₂₋₄ nitriles such as acetonitrile; ethers such as glyme and diglyme and cyclic ethers such as tetrahydrofuran and dioxane; tertiary amines, such as N-methylpyrrolidine and heterocyclic aromatic amines such as pyridine. and alcohols, most commonly the alcohol corresponding to the group R, for example methanol, ethanol, methoxyethanol, allyl alcohol or propargyl alcohol.

The process of the present invention is often carried out at a temperature of from room temperature, such as about 25°C, up to the reflux temperature of the solvent employed. Temperatures above the normal boiling point of the solvent employed can be employed if desired by carrying out the process under super-atmospheric pressure conditions, for example in a sealed reaction vessel. Commonly, the temperature is in the range of from 50 to 150°C.

The process commonly takes place over a period ranging from several hours, for example from 4 to 12 hours, to several days, for example from 1 to 2 days, depending on the reagents and reaction conditions employed.

When the compound of formula (1) comprises the base uracil, the uracil moiety may be converted to a cytosine moiety. Similarly, the uracil moiety comprised in the compound of formula (3) may also be converted to a cytosine moiety. The skilled man will recognise that a number of different techniques can be employed. Examples of such techniques include:

a) the nitrophenyl route (see Miah et al, Nucleosides and Nucleotides, 1997, 16, pp53-65) where for example the uracil containing compound is reacted with chlorotrimethylsilane in acetonitrile/1-methylpyrrolidine, then with trifluoroacetic anhydride, followed by 4-nitrophenol. The 4-nitrophenol moiety is then displaced with ammonia in aqueous dioxane to yield the cytosine-containing compound; and

b) the triazolation procedure, (see Divakar et al, J. Chem. Soc. Perkin Trans. 1, 1982, 1171-6) where for example the uracil containing compound is reacted with acetic

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anhydride in pyridine, then, after work up, with phosphoryl chloride, 1,2,4-triazole and triethylamine in acetonitrile to give the 4-triazolopyrimidine. The triazole moiety is then displaced with ammonia in aqueous dioxane, and acetyl groups removed to yield the cytosine-containing compound.

5 Protecting groups can be removed using methods known in the art for the particular protecting group and function. For example, acyl protecting groups, such as ethanoyl and benzoyl groups, can be removed by treatment with a solution of ammonia in an alcohol such as ethanol.

10 Benzoyl, pivaloyl and amidine groups can be removed by treatment with concentrated aqueous ammonia.

15 Trityl groups present can be removed by treatment with acid, for example a solution of dichloroacetic acid in dichloromethane. With regard to the overall unblocking strategy an important consideration is that the removal of trityl, often DMTr, protecting groups ('detritylation') should proceed without concomitant depurination when base B represents a purine, especially adenine. Such depurination can be suppressed by effecting 'detritylation' with a dilute solution of hydrogen chloride at low temperature, particularly ca. 0.45 M hydrogen chloride in dioxane - dichloromethane (1:8 v/v) solution at -50°C. Under these reaction conditions, 'detritylation' can be completed rapidly, and in certain cases after 5 minutes or less.

20 Silyl protecting groups may be removed by fluoride treatment, for example with a solution of a tetraalkyl ammonium fluoride salt such as tetrabutyl ammonium fluoride.

Fmp protecting groups may be removed by acidic hydrolysis under mild conditions.

25 The present invention is further illustrated, but not limited by, the following Examples.

General Experimental Details

30 Mps are uncorrected. ¹H and ¹³C NMR spectra were measured at 360.1 and 90.6 MHz respectively, with a Bruker AM 360 spectrometer; tetramethylsilane was used as an internal standard. TLC was carried out with Merck silica gel 60 F₂₅₄ pre-coated plates (Art 5715), which were developed in solvent system A [CHCl₃-MeOH (85:15 v/v)]. Short column chromatography was carried out on silica gel (Merck Art 7729). Acetonitrile and 1-methylpyrrolidine were dried by heating, under reflux, with calcium hydride and were then distilled. N,N-Dimethylacetamide (DMA) was dried by distillation over calcium hydride under reduced pressure. 2-Methoxyethanol was dried by heating with aluminium foil (1g/250ml), under reflux, and was then distilled. Diethyl ether was dried over sodium wire.

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Preparation of 2,2'-Anhydro-1-β-D-arabinofuranosyluracil

Uridine (12.21g, 50mmol), diphenyl carbonate (11.79g, 55mmol), sodium hydrogen carbonate (0.21g, 2.5mmol) and dry DMA (10ml) were heated together, with stirring, at 100°C. After 5h, the products were cooled to room temperature, and diethyl ether (100ml) was added with stirring. After 2 hours, the colourless precipitate (11.70g) was collected by filtration and was washed with ether (2 x 50ml). The sole nucleoside constituent of the precipitated material was identified as 2,2'-anhydro-1-β-D-arabinofuranosyluracil (calculated quantitative yield, 11.31g) by comparison with authentic material.

Preparation of 2'-O-(2-Methoxyethyl)uridine

Aluminium foil (3.64g, 0.135 mol) and dry 2-methoxyethanol (135ml) were heated, under reflux, for ca. 1hr until all of the aluminium had been consumed. Crude (see above) 2,2'-anhydro-1-β-D-arabinofuranosyluracil (10.18g, ca. 43.5 mmol) was added and the reactants were heated, under reflux, for 48 hours. Absolute ethanol (200ml), followed by water (7.3ml, 0.405mol) and Celite were added to the cooled products. The resulting mixture was heated, under reflux, for 10 minutes and was then filtered. The residue was washed with ethanol (3 x 100ml). The combined filtrate and washings were evaporated under reduced pressure to give a pale yellow solid. The material was purified by short column chromatography on silica gel (70g): the appropriate fractions, which were eluted with dichloromethane-methanol (90:10 v/v), were evaporated under reduced pressure to give the title compound as a colourless solid (12.05g, ca. 91%).

Preparation of 2'-O-(2-Methoxyethyl)cytidine

2'-O-(2-Methoxyethyl)uridine (6.05g, 20.0mmol), 1-methylpyrrolidine (20ml, 0.192mol), chlorotrimethylsilane (7.6ml, 59.9mmol) and dry acetonitrile (100ml) were stirred together at room temperature. After 1 hour, the reactants were cooled to 0°C (ice-water bath) and trifluoroacetic anhydride (7.1ml, 50.3 mmol) was added dropwise over 5 minutes. After a further period of 30 minutes at 0°C, 4-nitrophenol (8.35g, 60mmol) was added to the stirred reactants which were maintained at 0°C. After 3 hours, the products were poured into saturated aqueous sodium hydrogencarbonate (200ml), and the resulting mixture was extracted with dichloromethane (3 x 100ml). The combined organic layers were dried (MgSO₄), and evaporated under reduced pressure. Concentrated aqueous ammonia (d 0.88, 20ml) was added to a stirred solution of the residue in dioxane (100ml), contained in a sealed flask that was then heated at 55°C for 24 hours. The resulting yellow solution was concentrated under reduced pressure, and the residue was evaporated with absolute ethanol (3 x 50ml). The products were fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with

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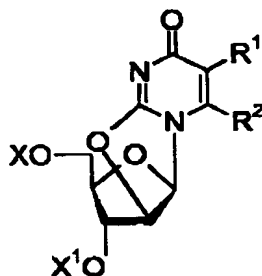
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dichloromethane-methanol-triethylamine (93:7:0.5 to 90:10:0.5 v/v) were evaporated under the reduced pressure to give the title compound as an off-white solid (5.07g 84%).

which comprises the reaction of a compound of formula (4)

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wherein

X, X', R¹ and R² are as defined above;

5 with a compound of formula Al(OR)₃ wherein R is as defined above, under substantially anhydrous conditions.

3. A process according to claim 2, wherein R¹ and R² are both H, or R¹ is C1-4 alkyl, and R² is H.

10 4. A process according to any preceding claim, wherein R is a C₁₋₄ alkenyl group, a C₁₋₄ alkyl group, a C₁₋₄ alkoxyC₁₋₄ alkyl group or a C₁₋₄ alkynyl group.

5. A process according to claim 4, wherein R is a methoxyethyl group.

15 6. A process for the preparation of a compound of Formula (1) wherein B represents cytosine, or a substituted derivative thereof, which comprises:

a) preparing a compound of Formula (1) wherein B represents uracil, or a substituted derivative thereof, by a process according to claim 1; and

20 b) converting the uracil moiety to the equivalent cytosine moiety; or

c) preparing a compound of Formula (3) by a process according to claim 2; and

d) converting the uracil moiety therein to a cytosine moiety.

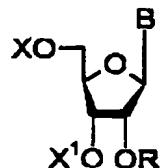
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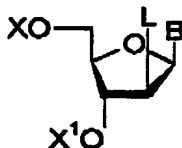
ABSTRACT2'-SUBSTITUTED RNA PREPARATION

A process for the preparation of a compound of formula (1):

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is provided, which comprises the reaction a compound of formula (2):



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with a compound of formula $Al(OR)_3$, wherein R is as defined above, under substantially anhydrous conditions. X, and X' are each independently H or a protecting group, B is a base; R is an alkyl, alkoxyalkyl, alkenyl, or alkynyl group, each of which may be optionally substituted, and L is a leaving group.

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Agent : Avecia Ltd.

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